Complications of Anti-reflux Surgery in Gastro-esophageal reflux disease with special reference to dysphagia.

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BRNABR003

Submitted to the University of Cape Town

In fulfilment of the requirements for the degree

MMed Surgery

Faculty of Health Sciences

University of Cape Town

Date of submission: August 2009

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DECLARATION

I, Abraham Justinus Brink, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Glossary

CI	Confidence interval
GABA	Gamma-aminobutyric acid
GORD	Gastroesophageal reflux disease
H pylori	Helecobacter pylori
H2 Blocker	Histamine 2 receptor blocker
LOS	Lower oesophageal sphincter
NERD	Non-erosive reflux disease
OGJ	Oesophago-gastric junction
PUD	Peptic ulcer disease
PPI	Proton pump inhibitors
tLOSr	Transient lower oesophageal sphincter relaxations

Review of literature

Definition of Gastroesophageal reflux disease (GORD)

GORD was defined by an international working group[1] as a disease caused by the reflux of gastric contents into the oesophagus leading to oesophagitis, reflux symptoms sufficient to impair quality of life, or risk of long-term complications. Non-erosive reflux disease (NERD) is a subcategory of GORD characterized by troublesome reflux-related symptoms in the absence of oesophageal mucosal erosions/breaks at conventional endoscopy and without recent acid-suppressive therapy[2].

Epidemiology of GORD

It is difficult to exactly determine the incidence and prevalence of GORD due to the different definitions and the substantial geographic variation. Different studies report prevalence of 0.7% to 5%[3]. There is a higher incidence in North America and Europe than in Africa and Asia[4]. Further more no good data are available for these figures in South Africa. The prevalence of GORD increases every year worldwide by approximately 4% and is now believed to be the most common affliction of the gastrointestinal tract. Certain epidemiologic factors such as longevity, obesity and use of medications conducive to lower oesophageal sphincter (LOS) relaxation, may partly explain the increased prevalence of GORD. Traditionally it was thought that men are more commonly affected than women, but a recent systematic review reported a similar period prevalence of heartburn in men and women[5]. Elderly patients are also noted to have a higher prevalence of GORD[4]. There is a positive association between body mass index of 25kg/m^2 or more and reflux symptoms. Genetic factors may also have a role in the disease. Two studies that have assessed the prevalence of reflux symptoms in monozygotic versus dizygotic twins gave more insight into the role of genetics in the

disease. Both studies reported significantly higher case-wise concordance rates for reflux symptoms in monozygotic compared with dizygotic twins[6, 7].

Complications of GORD include erosive oesophagitis, oesophageal ulcers, oesophageal strictures, and Barrett's oesophagus. These occur more commonly in men and elderly patients. The prevalence of erosive oesophagitis ranges from 0.7% to 1.2% in the general population. However, in patients with chronic GORD, the prevalence of erosive oesophagitis is estimated to be 20%[3]. Seventy to 80% of strictures occurring in the distal oesophagus are caused by GORD. The prevalence of strictures in the general population ranges from 0.07% to 0.12%. Patients with untreated erosive oesophagitis have a stricture rate between 7% and 23%.

Barrett's oesophagus is the only recognized risk factor for oesophageal adenocarcinoma[8]. The prevalence of Barrett's oesophagus is reported as 36.3% in patients with erosive oesophagitis compared with 12.4% in patients with GORD symptoms alone[9]. Barrett's oesophagus without dysplasia progresses to high-grade dysplasia in 5% of patients at 5 years. In contrast, low-grade dysplasia progresses to high grade dysplasia in 25% of patients at 5 years[10].

Clinical findings in Patients with GORD

Symptoms in patients with GORD are divided into oesophageal and extra oesophageal. Oesophageal symptoms consist of heartburn, regurgitation of stomach content, belching and bloating. The symptoms can be exacerbated by meals, exercise, or a change in posture. These symptoms may be progressive over years if the reflux goes unrecognised and can be replaced by dysphagia due to stricture formation. GORD is also a cause of atypical chest pain.

Extra-oesophageal symptoms include non-cardiac chest pain, laryngitis, chronic cough, hoarseness, abdominal pain, asthma, globus and dental erosions. Airway symptoms have

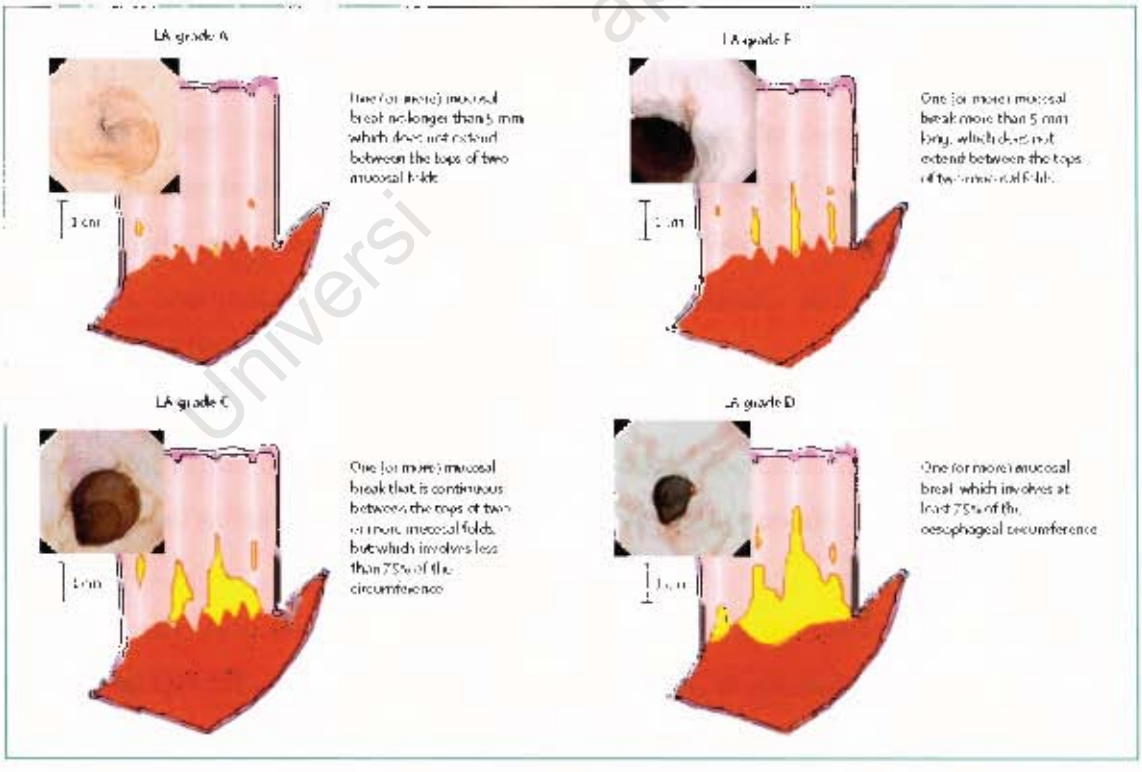
a common pathogenic mechanism that includes micro aspiration of acid into the larynx and pharynx, and vagally mediated bronchospasm and laryngospasm. In atopic patients, food allergy has been recently proposed as a possible cause of GORD and associated respiratory symptoms, and it should be considered in the diagnostic work-up of these patients[11]. The role of extra-oesophageal symptoms is often underestimated due to silent symptoms and difficult confirmation of the diagnosis. Anti-secretary therapy by proton pump inhibitor is used as both a diagnostic trial and as a therapy in the majority of these patients [12]. Physical examination rarely contributes to confirmation of the diagnosis, but is still necessary to identify possible signs of non benign disease or other disease processes.

Special investigations for GORD

Endoscopy is essential in confirming the diagnosis of erosive GORD and to exclude other disease processes of the oesophagus. Oesophagitis is graded with the Los Angeles Classification at our institution. In this classification Grade A represents one (or more) mucosal break no longer than 5 mm that do not extend between the tops of two mucosal folds. Grade B is when there are mucosal breaks more than 5 mm long that does not extend between the tops of two mucosal folds. Grade C represent one (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involves less than 75% of the circumference and grade D confirms one (or more) mucosal break that involves at least 75% of the oesophageal circumference (Figure 1). This classification was published in its definitive form in 1999 [13] and validated as the most reproducible and practical of all previous grading systems. It is the most widely used method for description of reflux oesophagitis used in the literature. Exclusion of minimal oesophageal mucosal change is, however, regarded as a significant limitation by some. Minimal change oesophagitis may now be recognized with high definition endoscopy and may need to be included in future modifications of the LA classification[14]. The gastro-oesophageal flap valve mechanism can be inspected by retroflection of the endoscope and this can also be graded. Hill *et al* modified this

grading system (Figure 2)[15]. The rest of the stomach and duodenum can also be inspected to rule out co existing pathology. The role of Helicobacter pylori infection in GORD is not completely clear. Eradication of Helecobacter pylori (H pylori) in duodenal ulcer or antral-predominant gastritis patients improves GORD symptoms in patients predisposed to GORD, whereas eradication in patients with corpus predominant gastritis sometimes worsens GORD in patients with a comparable degree of oesophago-gastric junction (OGJ) dysfunction. Although these phenomena may occur, it is important to emphasize that H pylori itself does not cause GORD and there is no association between H pylori eradication and development of new cases of GORD in the population of dyspeptic patients[16]. There are no data to suggest that H pylori have any role in altering tissue resistance, oesophageal clearance, or OGJ competence[4]. There seems to be a twofold higher risk of development of erosive GORD in patients with peptic ulcer disease (PUD)[16].

Figure 1: Los Angeles classification of oesophagitis[13]



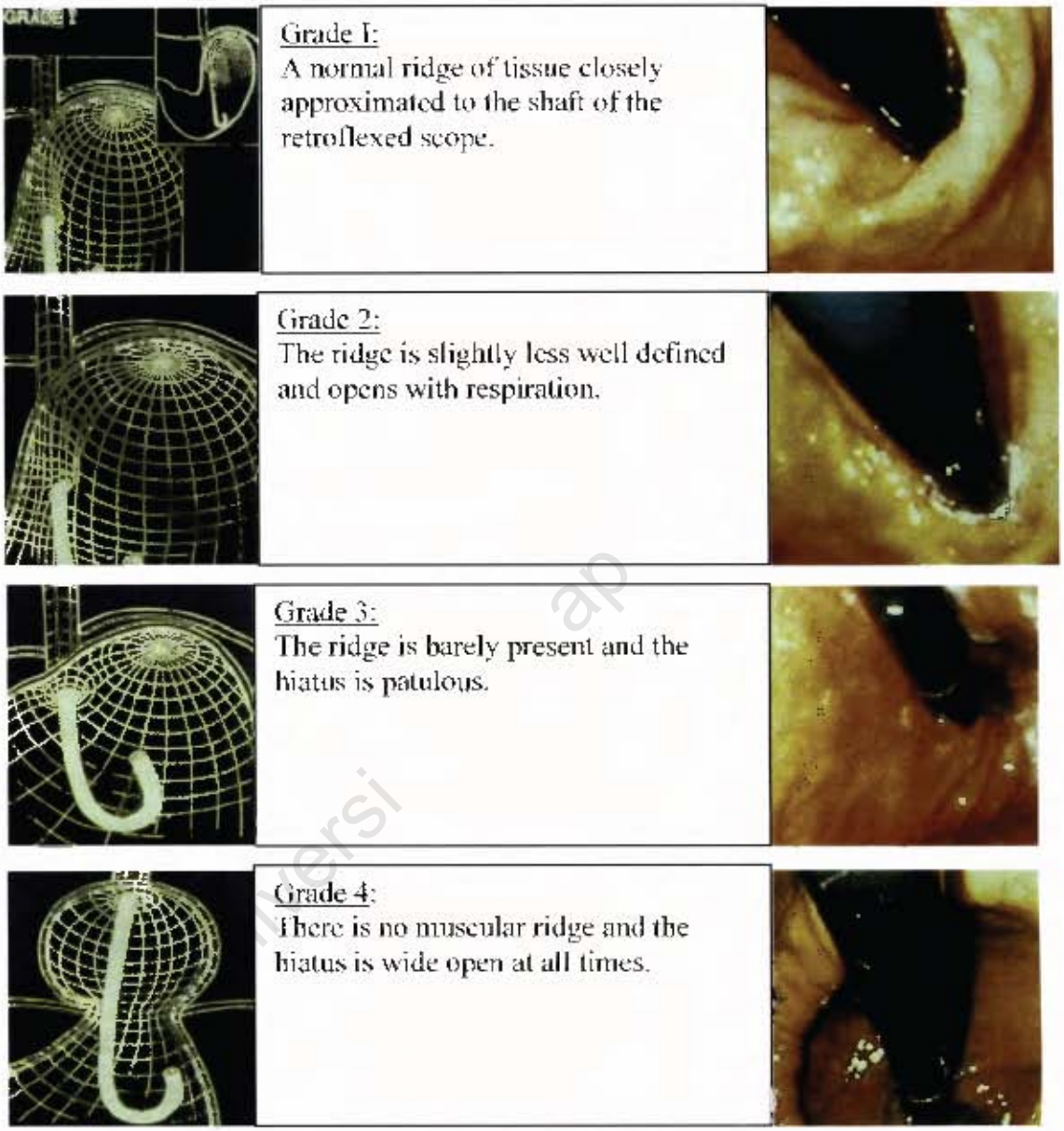
Manometry can assess total length, intra abdominal length and the location of the LOS relative to the nares. The normal resting pressure of the LOS is between 12 and 30 mm Hg. The body of the oesophagus can also be assessed for effective peristalsis. This is reported as a percentage of the initial swallow. Ineffective oesophageal motility or dysmotility is defined as less than 60% effective peristalsis or distal oesophageal amplitude of less than 30 mm Hg. Manometry can be done either at the bedside in a postprandial setting or using ambulatory manometry equipment. Manometry has focused on three dominant reflux mechanisms: transient LOS relaxations, without any necessary anatomic abnormality; LOS hypotension, without any anatomic abnormality; or anatomic distortion of the OGJ including hiatus hernia.

pH monitoring is used to diagnose and quantify acid reflux. A thin catheter containing a pH sensor is placed 5cm above the OGJ. Information is recorded in a 24 hour period and analysed by specialized software. The number of reflux episodes (pH < 4), longest episode, episodes lasting more than 5 minutes and extent of the reflux up the oesophagus all get recorded. The De Meester score is calculated from these values and if this score is above 14.27, the patient does have significant acid reflux. In the normal individual, acid reflux at pH less than 4, occur less than 4% of time in the distal oesophagus and less than 1% of time in the proximal oesophagus. Oesophageal pH monitoring has long been considered the gold standard for the diagnosis of GORD. In many patients, however, there is a poor correlation between acid reflux episodes and symptoms. The high prevalence of NERD and functional heartburn associated with normal oesophageal ph-metry are now recognised. Efforts have been made to detect all types of gastro-oesophageal reflux and to increase the likelihood of documenting the relation between symptoms and reflux events by prolonging the recording periods.

More recently, acid monitoring has been expanded from the conventional site at 5 cm above the LOS to include the entire oesophageal body. A wireless pH monitoring system has been validated as an alternative to catheter pH monitoring and shows better tolerability. Oesophageal impedance monitoring, combined with ph-metry, allows detection not only of acid reflux but also of weakly acidic and alkaline reflux and is

often used to assess gastro-oesophageal reflux in the postprandial period and in patients on proton pump inhibitor therapy with persistent symptoms[17].

Figure2: **Hill grading system of the gastro-oesophageal flap valve mechanism**[4]



Contrast study of the oesophagus is used to determine the anatomy of the oesophagus and proximal stomach. The presence and size of a hiatus hernia as well as a shortened oesophagus that may change the surgical approach can be demonstrated. Strictures, diverticulums, tumours and para-oesophageal hernias can also be revealed by this study.

Further, motility disorders can be detected with video oesophagography but not with endoscopy. It is recommended that most patients with co-incidental dysphagia initially undergo video oesophagography [18].

Scintigraphy is useful in patients that can not tolerate naso-oesophageal intubation. Oesophageal clearance and reflux can be demonstrated as well as delayed gastric emptying. This test is useful in paediatric surgery to evaluate patient for anti-reflux surgery and is frequently referred to as a milk scan.

Laryngoscopy can be done for patients with atypical symptoms. Inflammation, muscle tension abnormalities and subglotic stenosis are some of the findings in GORD.

Treatment

The symptoms of GORD can have a negative effect on quality of life[19]. It is also responsible for pathology in the oesophagus ranging from minor oesophagitis to ulceration, bleeding and strictures. Barrett's oesophagitis and adenocarcinoma of the oesophagus is also linked to this disease[20]. Treatment therefore is aimed at reducing acid production or altering the anatomy around the LOS. This can be achieved by medical, endoscopic or surgical methods.

Medical treatment

This includes diet and life style alterations. Simple antacids, selective Histamine 2 receptor blockers (H_2 blockers) and proton pump inhibitors (PPI).

Loss of weight, decreasing fatty foods, chocolates and foods that the patient knows gives symptoms are part of the dietary modification. Patients are also advised to avoid alcohol, caffeine and smoking of tobacco. Other modifications include not eating late at night and elevating the head of the bed. These alterations is in general part of a healthy lifestyle, but patients are not always compliant with these and there is no good evidence

that suggest they are effective in prevention of complications or changing the course of the disease[21].

Selective H_2 blockers and PPI work on the basis of decreasing the acidity of the gastric refluxate that reaches the oesophagus. PPI inhibit the activity of the gastric acid pump (H^+, K^+-adenosine triphosphatase), whereas H_2 blockers act at an early stage of the acid secretion pathway histamine receptors. PPI is superior in the treatment of GORD in particular with the healing of oesophagitis. PPI also have less side effects compared to H_2 blockers[22]. In patients with peptic oesophagitis, 90% will have completely healed on PPI in four weeks.

Minor side effects of selective H_2 blockers include constipation, diarrhoea, fatigue, headache, insomnia, muscle pain, nausea and vomiting. Major side effects are rare; they include: agitation, anaemia, confusion, depression, coagulation abnormalities, hallucinations, hair loss, arrhythmias, rash, visual changes and jaundice. They are still in use because they are relatively inexpensive.

Side effects of PPI are uncommon and include nausea, diarrhoea, headache, abdominal pain and rash. Long term effects include variations in bioavailability of common medications, vitamin B12 deficiency, *Clostridium difficile* associated diarrhoea, community-acquired pneumonia, hip fracture and gastric polyp formation[23]. These polyps are usually hyperplastic due to hypochlorhydric induced increase in gastric secretions and do not have malignant potential.

A significant proportion of patients on PPI report ineffective control of symptoms, the majority which result from ongoing high volume reflux of non-acid material. As reflux mainly occurs during transient LOS relaxations (tLOSR), drugs targeting this motor pattern may be of great interest to further reduce symptoms. Baclofen, a Gamma-aminobutyric acid (GABA) B receptor agonist, is the prototype of reflux inhibitors, reducing the number of tLOSR, reflux, and symptoms, but its central nervous system side effects are significant. Peripheral acting GABA (B) agonists will hopefully be

devoid of these side effects and are currently under study. Alternatively, antagonists to the metabotropic glutamate receptor 5 reported to reduce tLOSR and reflux may be of interest. Upcoming clinical trials with these reflux inhibitors will hopefully answer the question whether reflux inhibitors are indeed a new approach to treat GORD[24]. Prokinetics, like cisapride, as primary therapy have no benefit in the treatment of GORD[25].

Endoscopic treatment

Although appealing, endoscopic treatment has not been shown to be as effective or durable as medical or surgical treatment of GORD. Over the past decade, a number of endoscopic techniques have been developed as alternatives to medical and surgical treatment of GORD. The idea was to provide an outpatient trans oral, endoscopic procedure that would be effective in controlling reflux. Three major technologies emerged. Although each used a different approach to augment the barrier function of the lower oesophageal sphincter, mechanisms may be similar. These include:

Suturing involves using an endoscopic plicating devise that delivers a full-thickness transmural suture through the gastric cardia to restructure the anti-reflux barrier. Endoscopic full-thickness plication can reduce GORD symptoms and medication use for at least 3-years post-procedure. Treatment effect is stable from 1 to 3 years, and there are no long-term procedural adverse effects[26]. Comparing outcomes of the circumferential and helical plication patterns, study suggests that there is no benefit to additional plications when using the helical pattern[27]. There are no long term data available.

The Stretta procedure uses radiofrequency energy delivered to the tissues of the distal LOS and gastric cardia, which decreases LOS compliance, increases LOS muscle mass, and limits the inappropriate tLOSR responsible for GORD in many patients.

Enteryx, which is an inert polymer injected into the muscle layer of the OGJ has been withdrawn from the market.

To date, the underlying mechanism of action of these procedures has not been completely elucidated, although each alters the compliance of the OGJ and thus its ability to respond to a "refluxogenic stress". The target population currently consists of PPI-dependent GORD patients, with little or no hiatus hernia and without severe oesophagitis or Barrett's oesophagitis. The Stretta procedure is the only procedure to date to be subjected to a sham-controlled trial. Registries of complications suggest that these techniques are relatively safe, but serious morbidity and rare mortality have been reported. All can be performed on an outpatient basis. Future comparative studies with predetermined end points, validated outcome measures, prolonged follow-up, and complete complication registries are needed to determine the role of endoscopic procedures in the clinical practice of patients with GORD. Evolution of the current technologies will almost certainly occur, and a commonly performed, effective endoscopic antireflux procedure could possibly emerge. However, despite the potential benefits of these procedures, there is insufficient evidence at present to establish their safety and efficacy, particularly in the long term. The use of these procedures in the future will depend on improvements in the techniques themselves and on the emergence of high-quality data to demonstrate their long-term safety and efficacy. Clearly, there is a need for randomized control trails to compare endoscopic procedures with the currently accepted treatments for GORD, namely medical therapy and surgery. There is evidence to suggest that the observed benefits associated with some endoscopic procedures may be due to a placebo effect. It is important that future randomized control trails examine whether subjective measures of improvement, such as PPI use and quality of life scores, are supported by objective measures like oesophageal acid exposure.[28, 29]

Anti-reflux surgery

Philip Allison initiated the modern era of anti-reflux surgery. In 1951 he emphasized the altered physiology of the cardia as a reason for the symptoms of GORD and highlighted the incompetence of the oesophageal gastric junction as the aetiology for peptic oesophagitis. He focused on the crural sling for prevention of reflux. The technique he

used consisted of reducing the hernia, suturing the phrenoesophageal ligament and peritoneum to the abdominal aspect of the diaphragm and approximating the crural fibers behind the oesophagus. He also classified hiatus hernias into the sliding and rolling hernias now known as type 1 and 2 hiatus hernias. His technique had a good short term outcome but long term recurrence was high (49%)[30].

Norman Barrett, like Allison, also played a major role in changing the perception from only an anatomical abnormality to a physiologically based disorder in GORD. He focused on restoration of the cardioesophageal angle as the key element in prevention of reflux and this influenced operations developed by Hill and Belsey[31].

In 1936 Rudolph Nissen treated a 28 year old male with an oesophageal ulcer that penetrated into the pericardium. He performed a trans pleural mobilization and resection of the distal oesophagus and cardia with anastamosis of the oesophageal stump to the fundus. To prevent leakage of the anastamosis he implanted it into the anterior wall of the gastric body using the Witzel technique used for gastrostomies. On follow up of the patient Nissen observed that the patient reflux symptoms completely resolved. He did not use this technique specifically for GORD again and continued to use Harringtons and Allison methods as well as the Boerema gastropexy. In 1955 he used his experience from 1936 and performed his first fundoplication without an anastamosis on a 49 year old female patient with GORD symptoms. He published his first two cases in 1956 and called it gastroplication[32].

In the 1970's Nissen's fundoplication became the most popular anti-reflux procedure. This was modified by Nissen himself and other surgeons to get greater success rates and lower complication rates. Mario Rossetti, for example, elected not to divide the gastrosplenic omentum with the short gastric vessels. Partial fundoplications was also described by Andre Toupet (270° partial posterior fundoplication)[33], Thal (90° partial anterior fundoplication), Watson (120° anterior wrap) and Dor (150° - 200° anterior wrap). The length of the wrap also shortened to 2-3 cm. The laparoscopic Nissen fundoplication was first performed in 1991 by Geagea and Dallemagne *et al.*[34, 35]

Further modifications have subsequently been made by Donahue, DeMeester and Johnson consisting of dividing the short gastric vessels and minimizing the length of the wrap to 2 centimetres[31].

Due to these above modifications anti-reflux surgery has undergone major changes in the last decades. Procedures can be divided into open or laparoscopic and complete or partial fundoplications. Laparoscopic Nissen fundoplication (360 degree wrap or complete fundoplication) is the most commonly performed procedure. Partial fundoplications is mostly performed where achalasia of the oesophagus is also present. A Toupet (partial 250° posterior fundoplication) is used traditionally in patients with poor oesophageal peristalsis. This is no longer the case as Nissen fundoplication is also now used in these type of patients without and increase in the incidence of post fundoplication dysphagia[36]. A recent meta-analysis shows that partial fundoplication is a safe and effective alternative to total fundoplication, resulting in significantly fewer re-operations and a better functional outcome. The author cautions in the interpretation of the results of this meta-analysis due to the poor quality and the limited number of trials with long term follow up of the these trials[37]. Studies looking at post operative complications have shown that dividing the short gastric vessels when doing a Nissen fundoplication had no reduction in the post operative incidence of dysphagia or any other outcome variable[38]. Using a bougie while fashioning of the fundoplication also does not reduce the postoperative dysphagia rate[39]. Comparison between the open and laparoscopic approach is difficult due to only a few randomized controlled studies. If non randomized control trials are compared the incidence of post operative complications was reduced, the length of hospital stay was shorter and the return to full physical function was reduced in the laparoscopic group. Operating time was longer in the laparoscopic group in early studies and overall efficacy was the same. Due to the shorter in hospital stay laparoscopic anti-reflux surgery was more cost effective than the open procedures[38]. The success rate for the modern laparoscopic anti-reflux surgery range from 86% - 95% and the complication rate rang between 7% – 17% of cases. Patients with atypical symptoms, no response to acid reducing medication or morbid obesity should be informed of their higher risk of failure[40].

Both anti-reflux surgery and PPI are effective modern therapies for reflux disease, but both medical and surgical interventions have advantages and disadvantages. Taking oral PPI for life has few side effects but does not prevent volume reflux and the long term cost effectiveness is still controversial. Surgery has a short and long term complication and failure rate (Table 1)[41, 42]. There is a paucity of trials comparing surgery (even less with laparoscopic) with PPI therapy, but one report suggested that both were equally effective at controlling symptoms provided patients in the medical treatment group were allowed to increase the dose of drug to twice daily if necessary[43]. Other evidence exists to show that anti-reflux surgery is more effective than proton pump inhibition in the control of reflux-related symptoms at least in the short to medium term[44-46]. In terms of a risk-benefit analysis, the risk of an undesirable outcome or death from surgery exceeds that of maintenance treatment with PPI [47]. Neither therapy increases or reduces the risk of death from cancer. Instances in which surgery should be considered include: (1) Individuals who get side effects from PPI (2) Volume reflux (3) Young patients well controlled on PPI who cannot afford or who are unwilling to continue with long term medical treatment (4) Patients with limited access to PPI [47, 48]. Treatment decisions for GORD should be based on patient and surgeon preference.

Table 1. Early and late complications after laparoscopic Nissen fundoplication[41, 42]

Postoperative mortality	0.15 %
Perforations	1.0 %
Haemorrhage	1.1 %
Pneumothorax	2.0 %
Splenectomy	0.1 %
Early dysphagia	20 %
Dilatation/endoscopy	4.0 %
Late dysphagia	5.5 %
Reoperation for dysphagia	0.9 %
Reoperation for reflux	0.7 %
Ileus	6 %
Urinary retention	2 %

The most common peri-operative minor complications

Ileus is the most common and is even more common after revision surgery. This can be treated by inserting a naso-gastric tube. Hospital stay is not significantly longer in this group of patients.

Pneumothorax can be diagnosed intra-operatively and is also more common in revision surgery. It is usually not clinically evident and can be treated with supplementary oxygen and seldom need intervention with an intercostals chest drain. This is due to the CO2 being rapidly reabsorbed at the completion of the procedure.

Urinary retention can occur in both men and women. A catheter must be inserted and men must have prostate evaluation on discharge.

Other minor complications are atelectasis, pneumonia, atrial fibrillation and wound infection.

Major peri-operative complications

Acute herniation that needs immediate re-operation

Liver haematomas are common but are usually small and not seen as major complication. There are isolated reports of major bleeding from larger liver lacerations that needed transfusion and radiological embolization.

Perforation of a hollow viscus is more common with revision surgery. In cases where the perforation is only recognised postoperatively, immediately re-operation is indicated.

Other major complications include pulmonary embolism, injury to major vessels, mesenteric thrombosis and cardiac lacerations.

Long term complications

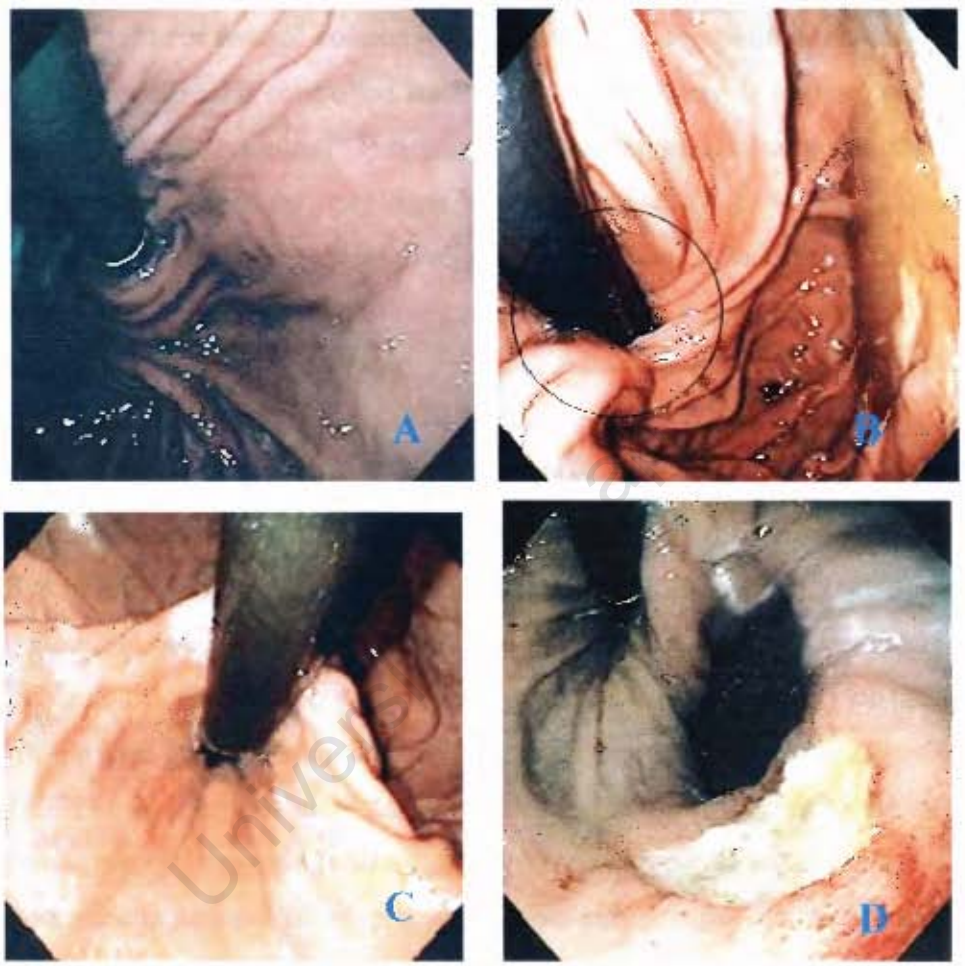
Long term complications manifest as symptoms that can be divided into two categories namely: (1) symptoms that are still present after the surgery for example heartburn, volume reflux, atypical chest pain, extra oesophageal symptoms and (2) new symptoms that is not due to gastro oesophagus reflux. New symptoms include bloating, diarrhoea and dysphagia[41, 49].

Management of these complications start with careful history taking. Symptoms that the patient describe as "heartburn" might not be related to GORD at all[50]. Therefore these symptoms will not be relieved by anti-reflux surgery. A specific description of the sensations and whether the sensation differs from the preoperative one is therefore essential. GORD can also be associated with functional symptoms that may not be related to the reflux of gastric content into the oesophagus. These functional symptoms include abdominal distension and fullness which might be part of a poorly defined gut motility disorder that predisposes to GORD[51]. Medical treatment or antireflux surgery will therefore not relieve these symptoms. Careful history taking can distinguish between a failed operation due to technical reasons or from failure of correct preoperative diagnosis[52].

After history taking endoscopy is used for objective evidence of reflux oesophagitis if the patient still complains of heartburn. Other pathological conditions that can cause the patients symptoms can be ruled out, for example oesophagus lesions or peptic ulcers. The fundoplication itself can be inspected with the endoscope in a retroflexed position for its location, orientation, span and the presence of a paraoesophageal herniation (figure 3D)[53, 54]. A Nissen fundoplication create characteristic folds in the proximal part of the stomach. The folds should be seen below the diaphragm (figure 3A). If the folds are located above the diaphragm it is indicative of a wrap that herniated through the hiatus (figure3B). A wrap that is too loose can also be diagnosed (figure 3C).

Radiological contrast studies are useful to ascertain the anatomical relationship of the fundoplication and other organs. Paraoesophageal herniations can be demonstrated and with post fundoplication dysphagia the radiologist can provide information on the efficacy of oesophageal emptying[52].

Figure3: Retroflexed endoscopic view of Nissen fundoplications: (A) Normal, (B) Wrap herniating through hiatus, (C) Loose wrap, (D) Paraoesophageal heria[54].



Ambulatory monitoring of the oesophagus pH can be used in patients with persistent reflux symptoms post fundoplication. It documents the pattern, frequency and duration of acid reflux and also establish a relationship between symptoms and episodes of reflux[55]. With this information it can be determined whether the patient's symptoms are due to a failed operation or not related to the surgery at all.

In patients with postoperative dysphagia, oesophageal manometry is useful to determine the presence of motility abnormalities.

Persistent reflux: Treatment for patients with persistent reflux can be medical (PPI) or surgical. There are no randomized trials to compare these two therapies. Long-term follow-up studies demonstrate that up to 62% of patients will require intermittent anti-reflux medications to control symptoms[56]. PPI are highly effective for these patients but again it will not control volume reflux. There is no compelling reason to re-operate if the symptoms are well controlled on PPI even when there is a clear technical correctable reason for the symptom. Patients who have atypical symptoms that persist despite adequate PPI therapy may have a functional disorder or other reasons for there symptoms that will not respond to re-operation[52]. Patients with a clear technical correctable reason for the symptoms, but do not respond well to PPI need revision surgery.

Gas bloat syndrome: The gas bloat syndrome is a constellation of symptoms that is presumably a result from inability to vent gas from the stomach into the oesophagus. Symptoms include bloating, abdominal distension, early satiety, nausea, upper abdominal pain, flatulence, inability to belch and inability to vomit. The cause for the syndrome is not clear, but is believed to be due to the inability of the GOJ to relax in response to gastric distension[57]. Aerophagia that is a symptom of patients with severe GORD may continue after the fundoplication and this aggravate the situation further[58]. Impairment of the meal induced receptive relaxation and accommodation of the stomach with accelerated gastric emptying can also play a role[59]. Other theories include: small intestinal bacterial overgrowth, surgical injury to the vagus nerve which delays gastric emptying and impairment of the transient LOS relaxation that is part of the normal belch reflex [60].

The incidence of post fundoplication gas bloat syndrome range between 19% and 80%[57, 61]. A minority of patients will develop severe, persistent symptoms which may interfere with their overall quality of life[62]. Interestingly up to 60% of patients that are started

only on PPI therapy without any surgery can report gas bloat symptoms in the first year of treatment[57]. Treatment for gas bloat syndrome range from dietary modifications to avoid gas producing food, gas reducing agents such as simethicone, prokinetic agents such as metroclopramide and advise to avoid aerophagia[63]. There are no evidence to support any of these treatments, but the patient can be reassured that these symptoms usually disappear within six months[61]. For patients with debilitating gas bloat symptoms after fundoplication, other pathology must first be excluded. These include small bowl obstruction due to e.g. adhesions, gastric outlet obstruction caused by e.g. peptic ulcer disease and vagal nerve injury that will delay gastric emptying. The first two are usually easy to exclude with readily available special investigation, but excluding vagal nerve injury can be difficult. Radionuclide test can document delayed gastric emptying and suggest vagal nerve injury[64]. Other functional tests include Congo red test, sham-feeding with gastric acid analysis and sham-feeding with measurement of plasma pancreatic polypeptide levels[65, 66]. These tests are no longer widely performed. Patients that do have delayed gastric emptying also have several treatment options. They should be advised to eat frequent smaller volume meals low in fibre and fat. Prokinetic agents have been recommended although little evidence exists for there usefulness in delayed gastric emptying post fundoplication. There are case reports of patients treated by injecting Botilinum toxin into the pylorus via gastroscopy[67]. In extreme cases the patient will need surgical pyloroplasty or gastroenterotomy. Unfortunately no preoperative tests can predict which patients will benefit most from this invasive procedures.

Diarrhoea: Diarrhoea occur in up to 33% of patients post fundoplication[68]. The exact cause is not known. This relatively high incidence may be due in part to pre-existing irritable bowel syndrome, which commonly coexists in patients with GORD[51]. Onset can be delayed for up to 6 months postoperatively and sometimes persisting for several years. Patients who undergo concomitant cholecystectomy are at a higher risk for this complication and up to half may experience postoperative diarrhea[61]. Those with significant diarrhea may also experience weight loss. Malabsorption diarrhea can result from injury to the vagus nerve with subsequent decrease in pancreatic secretions[63]. The same nerve injury may also result in small bowel dysmotility leading to bacterial

overgrowth. An additional mechanism resulting in diarrhea involves increased gastric emptying and reduced gastric accommodation leading to a more rapid intestinal transit time. Contributing dietary factors include the consumption of liquid and bland diets. Clinical symptoms usually manifest as explosive diarrhea occurring postprandially[62]. This may be associated with anorectal incontinence, thus raising the level of anxiety in the patient and physician. Persistent symptoms require further evaluation including, but not limited to, workup for infectious diarrhea, celiac disease, bacterial overgrowth, as well as possible endoscopic/radiological evaluation. There is no specific treatment for this and management is empirical. Use of anti diarrhoeal medications, along with dietary modification (e.g. fiber supplementation and avoidance of gas-forming foods) and reassurance usually provides adequate relief of symptoms in most patients[63]. Cholestyramine and anti-motility drugs may also be useful.

Dysphagia: Dysphagia after anti-reflux surgery occurs commonly during the early post operative phase. In 50% of patients this is significant enough so that they have to take precautions with meals. In the majority of cases this resolves after 3-6 weeks but in 5 – 10% this may persist[69]. The cause for dysphagia may be multifactorial. Possible causes include ongoing acid reflux with peptic oesophagitis, tightness or a twisted wrap, over zealous crural repair, re-herniation, secondary achalasia and peri-oesophageal fibrosis[70] (Table 2). Determining the exact underlying cause(s) can be problematic even after exhaustive investigation by means of a barium meal (with or without a solid bolus), gastroscopy, manometry and radio-isotope studies. The evaluation of these patients can be further compounded by subjective perceptions they have of their symptoms[71].

Table 2: Causes for persistent post fundoplication dysphagia[70]

GORD related
Peptic oesophageal stricture
Recurrent reflux oesophagitis
Mecanical obstruction
Fundoplication to long, twisted or to tight
Slipped fundoplication
Para-oesophageal hernia
Peri-oesophageal fibrosis
Reherniation
Over zealous crural repair
Oesophageal motility disorders
Ineffective oesophageal motility
Achalasia missed preoperatively
Achalasia developed postoperatively

There is a wide range of treatment options depending on the pathology. As previously mentioned reflux oesophagitis can be treated conservatively with PPI. With peptic strictures dilatation therapy should be performed[70]. Dilatation is also performed in patients with mechanical obstruction where the integrity of the fundoplication and its correct position can be demonstrated. Pneumatic dilatation seems to have a more favourable outcome than bougie dilatation and results of success varies between 60 – 70%. Raised nadir LOS relaxation pressure seems to be a useful predictor of successful outcome[72]. Only about 25% of patients who had a successful first dilatation require further intervention. Patients are usually dilated to a mean of 18 mm and can be done within the first week after the fundoplication[73]. Dilatation normally fails for slipped fundoplications, para-oesophageal herniation[70] and peri-oesophageal fibrosis (see study in this text). In these cases re-operation is usually necessary for obstruction symptoms.

Surgical intervention may vary from releasing of peri-oesophagus fibrosis to revision of the wrap or even oesophagectomy[74, 75]. The overall success of revision surgery for dysphagia is less than other indications[75, 76]. Low-amplitude distal oesophageal contractions, intrathoracic wrap migration and an abdominal approach are significant predictors of an unsuccessful symptomatic outcome after re-operation for troublesome dysphagia[77].

Revision surgery

Preoperative workup before re-operation is not standardized but tailored according to the cause of failure and the indication for re-operation and consists of the modalities mentioned in the management of complications. The revision rate after anti-reflux surgery is as high as 17%[78]. The most common indications as mentioned before are listed in table 3, with recurrence of reflux having the highest incidence. In a recent detailed meta-analysis of reported studies which deal with

Table 3: Indication for revision.

Recurrent reflux
Dysphagia
Recurrent reflux and dysphagia
Anatomical abnormality
Gas bloat syndrome

the failures of antireflux surgery and revision surgery the most common cause found for failure of the index surgery was wrap migration[79]. Other causes are listed in table 4.

Table 4: Causes for failure of previous antireflux procedure[74].

Anatomical abnormalities	
Intrathoracic wrap migration	27.9%
Wrap disruption	22.7%
Telescoping	14.1%
Para-oesophageal hiatal herniation	6.1%
Hiatal disruption	5.3%
Tight wrap	5.3%
Stricture	1.9%
Wrong primary diagnosis	
Achalasia	1.2%
Oesophageal spasms	0.2%
Sclerodermia	0.1%
Oesophageal carcinoma	0.03%
Disturbed oesophageal motility	0.4%
No cause for failure identified	6.1%
Miscellaneous	10.9%
Not reported	3.8%

In a literature review, revision surgery was performed laparoscopically, by open abdominal and via a thoracotomy approach in 36.3%, 34.7% and 22.7% of cases respectively[79]. The symptomatic outcome after re-operation is reported successful in 81% of patients. The mean symptomatic success rate of laparoscopic and the conventional abdominal approach is the same, but the mean objective success rate of laparoscopic re-operation seems higher than in the case of a conventional abdominal approach (85.8±5.6% and 78.0±10.1%, respectively)[79]. A laparoscopic approach for re-intervention provides excellent subjective and objective outcomes in most patients[75], but re-operation is more challenging that the initial repair, the success rate for symptom control is lower (between 62% and 93%[49, 74]) and appears to decrease with subsequent re-operations[80]. Comparing the outcome of total and partial refundoplication, one study reported symptomatic success in 68% and 60% of patients[81] respectively. In two other studies however, no relationship between the type of fundoplication and the symptomatic outcome was demonstrated[82, 83].

Predictors of a poor result after revision surgery include those with low-amplitude distal oesophageal contractions, intrathoracic wrap migration, an abdominal approach, those with dysphagia, those requiring oesophagus lengthening procedures and those who had previous Collis gastroplasty[74, 75, 77]. The mortality rate is also higher that that of the primary repair. (0,1% vs. 0.5%)[38, 74]. Morbidity was most frequently caused by direct

injury of the oesophagus and stomach during re-operation mainly as a result of increased complexity due to adhesions after the primary operation[79].

Oesophagectomy or gastrectomy (although rare) might also be necessary. The reasons to perform oesophageal resection are severe oesophagitis with or without Barrett metaplasia, peptic stricture of the oesophagus, severely disturbed oesophageal motility, or short oesophagus. Gastric resection is performed in cases with alkaline reflux, dense adhesions on attempted refundoplication, or severe gastric paresis[79].

Peri-oesophageal fibrosis, an important cause for persistent dysphagia after anti-reflux surgery

Aim of study

We report the outcome of revision surgery for intractable dysphagia post laparoscopic Nissen fundoplication in a subgroup of patients in whom peri-oesophageal fibrosis was identified as the main underlying cause, an entity which has hitherto not been clearly documented. In one of the largest reviews on this topic, no mention is made of peri-oesophageal fibrosis as a cause of post-operative dysphagia[84].

Materials and methods

All patients who underwent revision laparoscopic surgery from January 2002 to July 2008 in the UCT Private Academic / Groote Schuur Hospital complex for intractable dysphagia and who did not respond to conservative treatment were reviewed. Patients with peri-oesophageal fibrosis as the dominant cause for their dysphagia were identified during surgery and closely followed up. The study was focussed on these patients' pre- and post-operative course. The follow-up of patients who had revision surgery for other causes was incomplete and where therefore excluded from this study.

Pre-revision investigations included barium swallow, endoscopy and in selected cases manometry. Surgery entailed release of the peri-oesophageal fibrosis via a laparoscopic approach with or without revision of the fundoplication. Patients were followed up to assess their outcome in terms of dysphagia, recurrent gastro-oesophageal reflux disease (GORD), regurgitation and chest pain. These were graded by a numerical scoring system pre and post revision surgery (Appendix 1). A validated Gastro-oesophageal Reflux Disease-Health Related Quality of Life (GORD-HRQOL) questionnaire[19] (Appendix 2) was also completed where feasible. Data are reported as mean (95 per cent confidence interval (CI)) or median (range). Paired data were analysed using the Wilcoxon

matched-pairs signed-ranks test. Statistical significance was accepted at $P < 0{,}050$. This study was approved by the Research and Ethics Committee of the University of Cape Town.

Results

Fifty-three patients had revision surgery performed after anti-reflux surgery during the study period (figure 4). The main indication for revision was dysphagia in thirty two (60%) of these patients. Out of the 32 patients with dysphagia, seventeen (53.1%) had peri-oesophageal fibrosis as the predominant cause for persistent dysphagia. The operative findings in the recurrent reflux and dysphagia groups are indicated in table 5 and 6 respectively.

Figure 4: Flow diagram illustrating the different indications for the revision surgery.

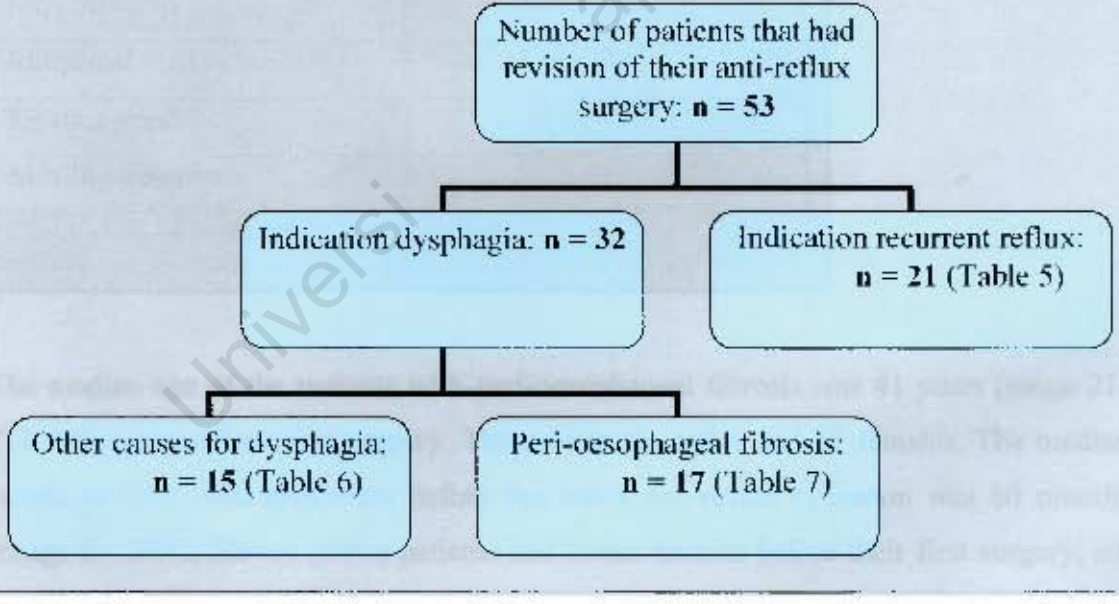


Table 5: Breakdown of the different causes for recurrent reflux found during surgery.

Recurrent reflux causes	n = 21
Recurrent hiatus hernia	9
Para-oesophageal herniation	3
Slipped wrap	3
Idiopathic	2
Motility disorder	2
Oesophageal diverticulum	1
Wrap came undone	1

Table 6: Breakdown of the different causes found for dysphagia after anti-reflux surgery.

Dysphagia causes	n = 32
Peri oesophageal fibrosis	17
Herniation of wrap into chest	3
Tight wrap	3
Tight crural repair	2
Slipped wrap	2
Idiopathic	2
Fibrotic band	1
Motility disorder	1
Carcinoma of stomach	1

The median age of the patients with peri-oesophageal fibrosis was 41 years (range 21-71) at the time of revision surgery. There were six males and 11 females. The median length of time with symptoms before the index anti-reflux operation was 60 months (range 8 - 240). Eleven (64%) patients had hiatus hernias before their first surgery, six (35%) had oesophagitis and four (24%) had Barrett's oesophagus. Their mean combined heartburn and reflux score was 5.4/8 (95 per cent CI 4.5 to 6.3) and of the 12 patients who completed the quality of life (QOL) questionnaire the mean score was 28.3/50 (95 per cent CI 25.7 to 35.6) before the index anti-reflux operation. All patients had previous

laparoscopic Nissen fundoplications. The demographics for the patients with predominantly peri-oesophageal fibrosis are depicted in table 7.

Table 7: Demographics of the patients that had peri-oesophageal fibrosis as a cause for there dysphagia.

Number of patient with peri-oesophageal fibrosis as cause for dysphagia	n = 17
Mean age (range)	41 years (21-71)
Male : Female	6 : 11
Average length of time with symptoms before first surgery (range)	88 months (4-240)
Average length of time between first surgery and revision surgery (range)	10 months (2-42)

The median length of time before the revision surgery was 5 months (range 2 – 42). Three (18%) patients had already undergone revision surgery for recurrence of heartburn. In eight (47%) patients the dysphagia started immediately following surgery, five (29%) had onset less than a week post surgery and four (24%) developed dysphagia when solids were introduced to their diet. Dysphagia was persistent and severe in all of these patients with a mean dysphagia score of 9.1/12 (95 per cent CI 7.4 to 10.8) and a mean weight loss of 14.04 kg (95 per cent CI 12.1 to 16.0) before revision surgery. Their mean disease specific quality of life score was 16.2/50 (95 per cent CI 10.6 to 21.8) before revision.

Twelve (75%) of the 16 patients who had contrast studies showed overt hold up of contrast at the OGJ as illustrated in figure 5. In 10 of the 12 patients who had endoscopy, resistance or frank stenosis was noted at the OGJ. Of the eight patients who had manometry studies; four were normal, two showed partial relaxation of the LOS and in two there was no relaxation. None of these patients had absent peristalsis (Figure 6). None of the patients had pH studies before there revision surgery. Eleven patients had balloon dilatations before their revision surgery (twice in 3 patients) without appreciable improvement.

Figure 5: Barium swallow of a patient with peri-oesophageal fibrosis:

(A) Before revision and (B) after revision surgery.

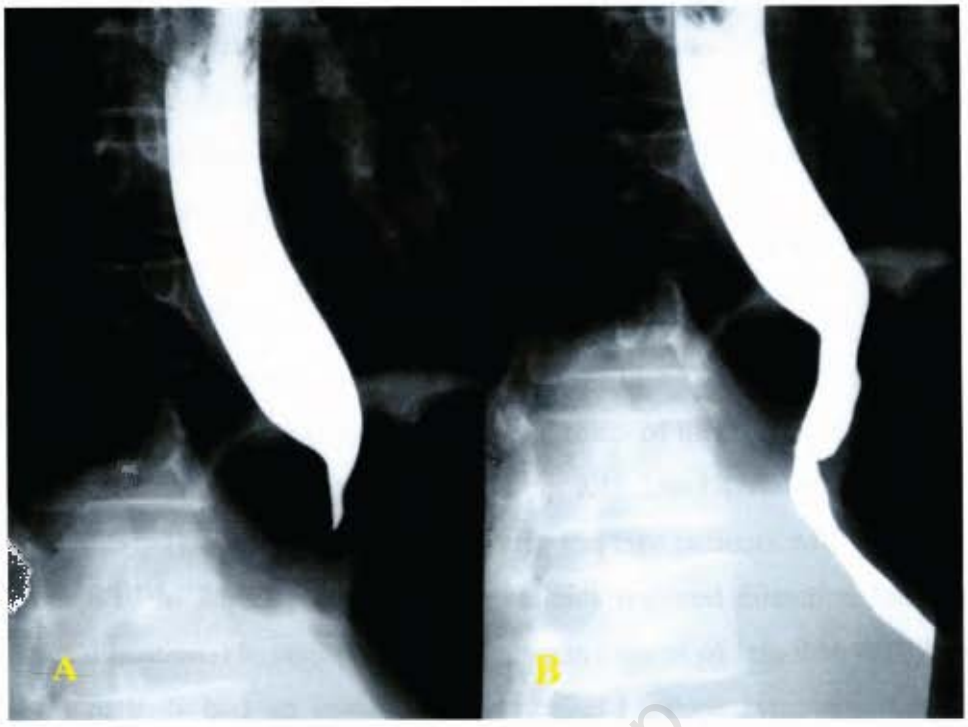
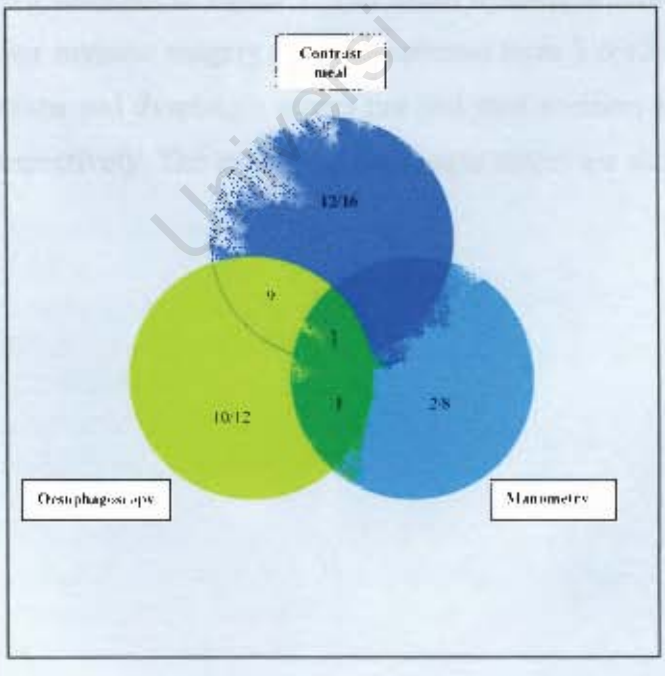


Figure 6: Pre revision investigations with green showing the number of oesophagoscopies that had resistance to the scope, blue showing the number manometries that had no LES relaxation and purple showing number contrast meals that had hold up.



At revision surgery, all 17 patients had marked peri-oesophageal fibrosis that was judged to be the main cause of their dysphagia. In one patient there was an additional tight crural repair. All but two patients had their revision operations done laparoscopically. Eight patients had release of the peri-oesophageal fibrosis while the remainder had an additional revision of the fundoplication (Seven anterior and two Nissen fundoplications).

The median post-operative follow-up was 49 (7-84) months. Twelve (70.6%) patients had complete and five (29.4%) had partial relief of their dysphagia shortly after surgery. The mean dysphagia score improving from 9.1/12 to 1.1/12 (95 per cent CI 0.3 to 1.9) ($p = 0.0003$). The mean dysphagia score in the five patients with partial relief improved from 8/12 to 2.6/12. Three of these patients required dilatation intermittently (two to three dilatations) to control minor dysphagia (scores of less than 4/12 before dilatation). Two patients had an initial complete relief of their symptoms but developed mild dysphagia again on subsequent follow-up with dysphagia scores of 3/12. In one patient the dysphagia was mild enough to decline further intervention while the other patient opted for a dilatation which resolved the dysphagia completely. This is illustrated as a flow diagram in figure 7. The mean dysphagia score in all patients that had dilatations after revision surgery further improved from 3.6/12 to 2/12 ($n = 4$). The mean symptom scores and dysphagia scores pre and post revision surgery are shown in figure 8 and 9 respectively. The individual dysphagia scores are shown in figure 10.

Figure 7: Flow diagram illustrating the course of the 17 patients with peri-oesophageal fibrosis as cause for their dysphagia

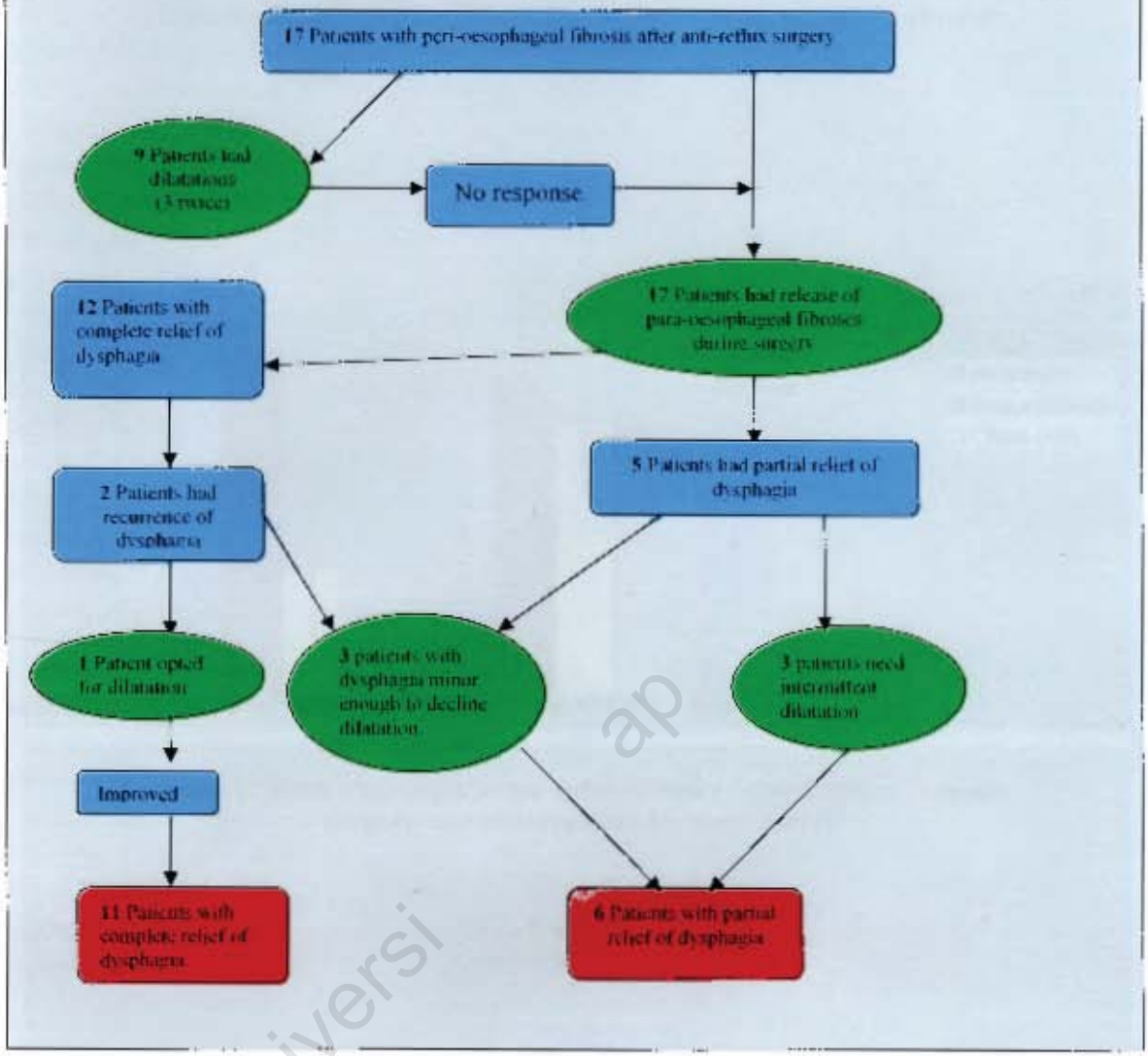


Figure 8: Mean symptom scores before index surgery, before revision surgery and after revision surgery. (n=17)

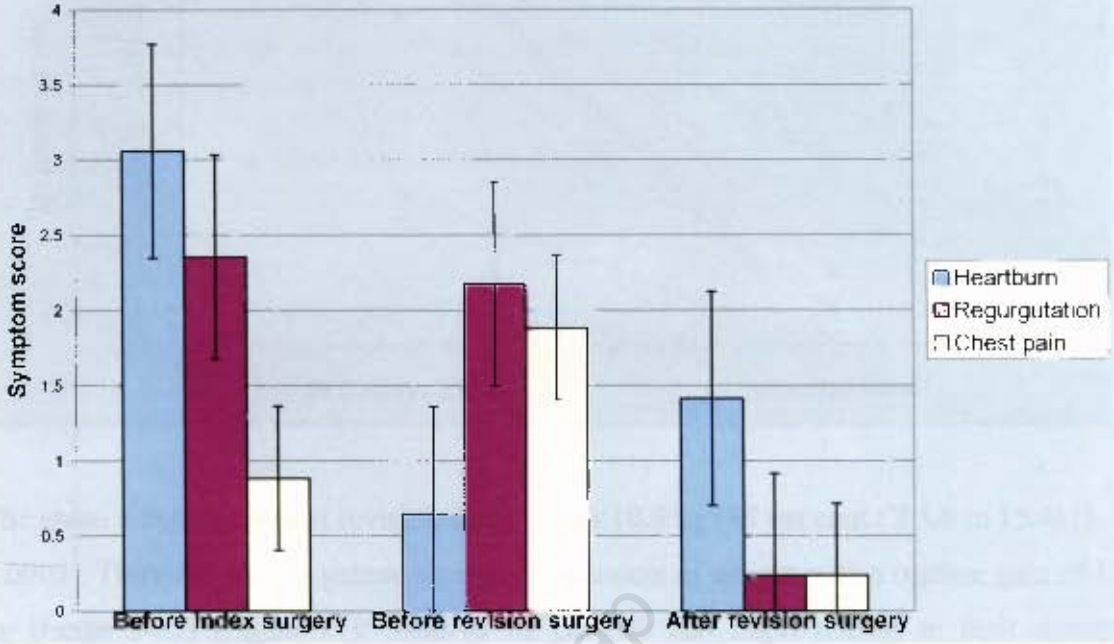
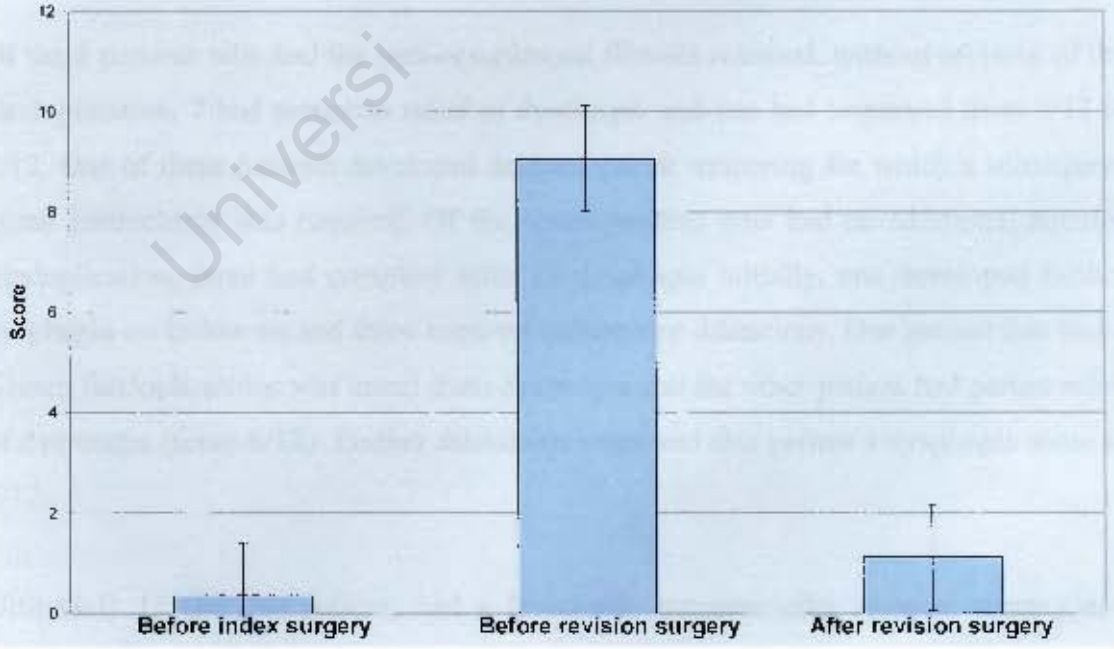
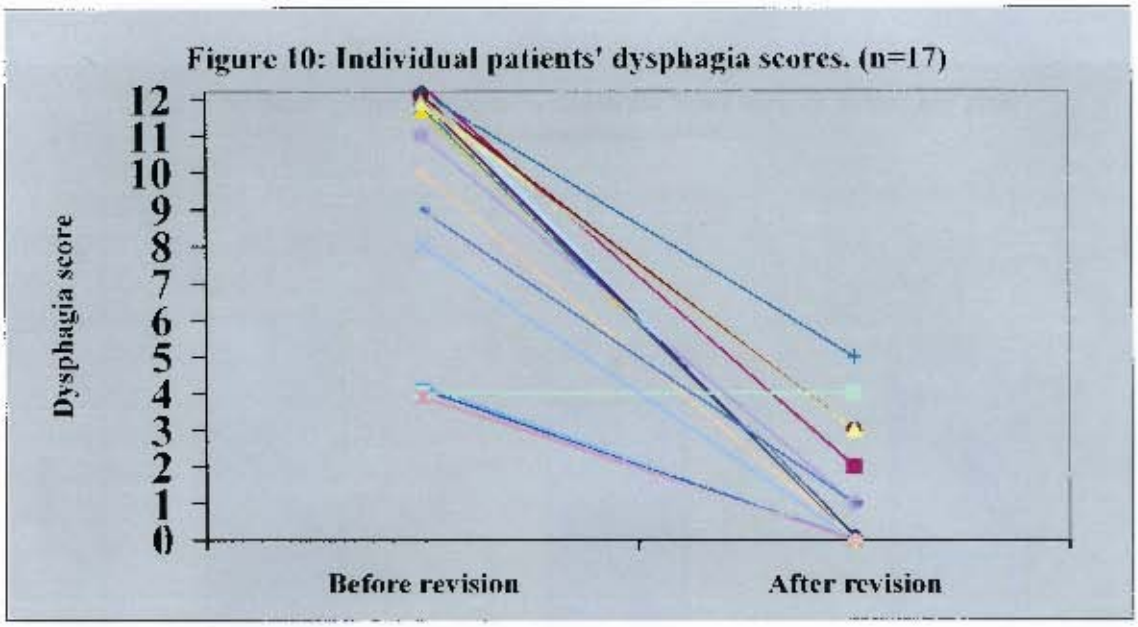


Figure 9: Mean dysphagia score before index surgery, before revision surgery and after revision surgery. (n=17)





The mean weight gain post revision surgery was 10.5 kg (95 per cent CI 5.6 to 15.4) (p = 0.0007). Thirteen patients gained significant amounts of weight with a median gain of 11 kg (range 5-33) (figure 11). Nine of 12 patients had improvement in their disease specific quality of life score (figure 12). The mean QOL score for all patients improved from 19.6/50 to 10/50 (95 per cent CI 5.5 to 14.4) (P = 0.0453).

Of the 8 patients who had the peri-oesophageal fibrosis released, without revision of the fundoplication, 7 had complete relief of dysphagia and one had improved from 4/12 to 2/12. One of these patients developed delayed gastric emptying for which a subsequent distal gastrectomy was required. Of the seven patients who had an additional anterior fundoplication, three had complete relief of dysphagia initially, one developed further dysphagia on follow up and three required subsequent dilatations. One patient that had a Nissen fundoplications was cured from dysphagia and the other patient had partial relief of dysphagia (score 6/12). Further dilatations improved this patient's dysphagia score to 5/12.

Ultimately 15 (88.2%) patients had a favourable outcome after revision surgery and dilatation in those with residual dysphagia

Figure 11: Mean weight in kilograms before the index surgery, before and after the revision surgery. (n=17)

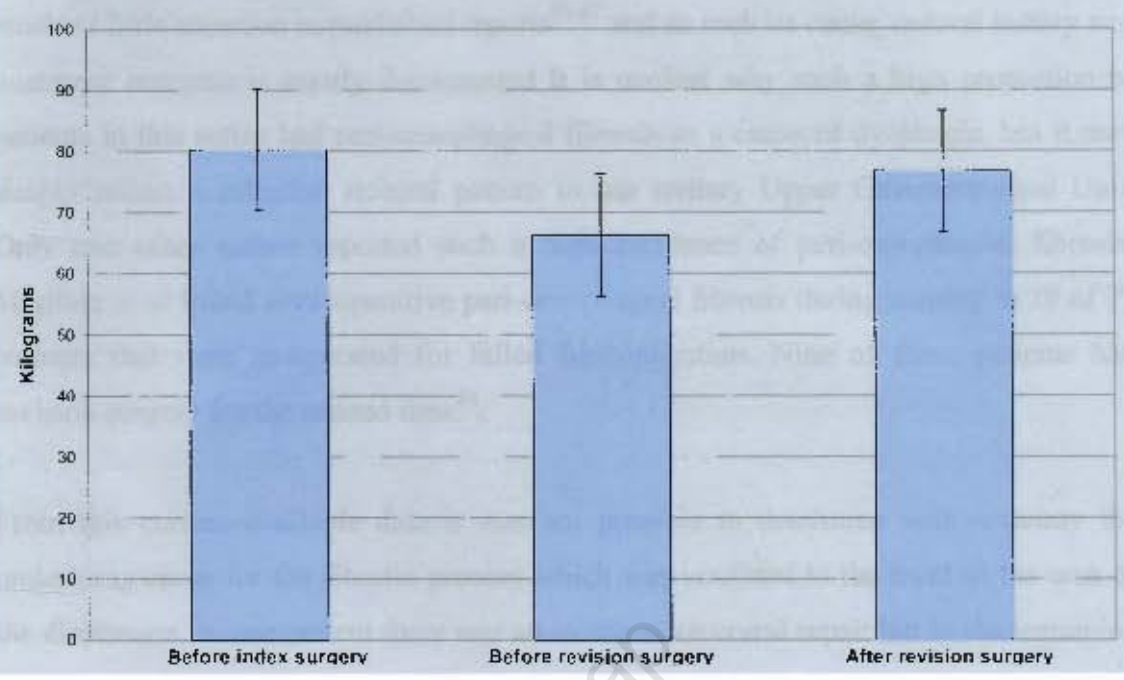
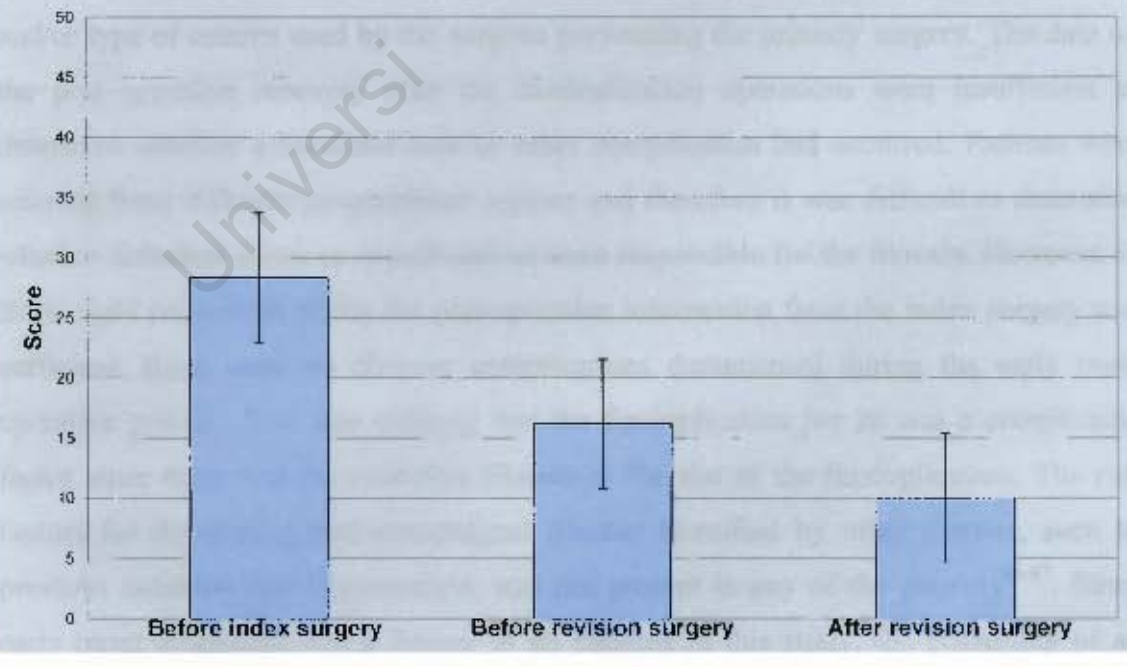


Figure 12: Mean GERD-HRQL score before index surgery, before revision surgery and after revision surgery. (n=12)



Discussion

Peri-oesophageal fibrosis as a cause of dysphagia after anti-reflux surgery has so far received little attention in published reports[84-87] and as such its cause, natural history and treatment outcome is poorly documented It is unclear why such a high proportion of patients in this series had peri-oesophageal fibrosis as a cause of dysphagia, but it may simply reflect a selective referral pattern to our tertiary Upper Gastrointestinal Unit. Only one other author reported such a high incidence of peri-oesophageal fibrosis. Migliore *et al* found intra-operative peri-oesophageal fibrosis during surgery in 19 of 77 patients that were re-operated for failed fundoplication. Nine of these patients had revision surgery for the second time[88].

From this current available data it was not possible to determine with certainty the underlying cause for the fibrotic process which was confined to the level of the crus of the diaphragm. In one patient there was an overzealous crural repair but in the remaining patients this was not observed. What makes this possible explanation less likely is the fact that the fibrotic process was circumferential and distant from the crural repair sutures. The data also lacked sufficient information to implicate the method of dissection and/or type of sutures used by the surgeon performing the primary surgery. The data on the post-operative recovery after the fundoplication operations were insufficient to determine whether a localized leak or other complication had occurred. Patients were referred from different geographical regions and therefore it was difficult to determine whether technical errors or complications were responsible for the fibrosis. However, in those eight patients in whom the peri-operative information from the index surgery was sufficient, there were no obvious complications documented during the early post-operative period. It is also unlikely that the fundoplication *per se* was a contributing factor since there was no excessive fibrosis at the site of the fundoplication. The risk factors for developing peri-oesophageal fibrosis identified by other authors, such as previous radiation and fibromyalgia, was not present in any of the patients[85-87]. Since early onset dysphagia was a feature in all patients in this study, the possibility of an ischaemia process of the crura should be considered.

The clinical course in these patients was characterized by early onset and protracted dysphagia, the severity of which was reflected by profound weight loss and impaired QOL when assessed objectively in 12 of the patients.

Patients underwent a variety of special investigations prior to referral which, together with there clinical course, dictated to a certain extent the need for additional studies. A possibly criticism of this study is the lack of a complete work-up with barium contrast studies, endoscopy, manometry and isotope studies in all patients before revision surgery was carried out. However, while logistical and financial constraints had to be factored into the decision making, significant weight loss and objective evidence of a mechanical hold-up on barium contrast studies and/or endoscopy was regarded as sufficient to make a decision for a revision operation. Nevertheless, in eight patients the exact cause was not diagnosed until the time of surgery, a problem which is well recognized and documented in other studies[86]. Even motility studies in this series were of poor discriminatory value, although the numbers were small.

While the success rate of balloon dilatation for dysphagia after anti-reflux surgery is purported to be 60-70%, these were obtained in a group of patients where peri-oesophageal fibrosis was not a predominant feature[72]. The poor results achieved in the eleven patients who had pre-operative balloon dilatation have discouraged the unit to offer this as a routine before surgery was contemplated. Considering the severity of the fibrosis, it comes as no surprise why even forceful balloon dilatation failed to alleviate the dysphagia in these patients.

Unlike with revision operations for recurrent hiatus hernias, these operations are relatively easy to perform by a laparoscopic approach. The use of an ultrasound dissecting devise greatly facilitates the procedure. In addition, the use of intra-operative endoscopy provides reassurance by excluding residual oesophageal stenosis and perforation of the oesophagus and stomach. Simple release of the fibrosis was performed

in almost half of the patients and produced the best results. The reasons for the higher rate of residual dysphagia in those who had a revision fundoplication are unclear.

The decision to take down the fundoplication was mainly for a poorly constructed wrap or to facilitate mobilization of the oesophagus. Likewise the choice between an anterior (Watson) or Nissen procedure to reconstruct the fundoplication was based on technical considerations. Anterior fundoplication became the preferred procedure during the study period based on the assumption that the risk of recurrent dysphagia related to the fundoplication should be less with this operation.

The post-operative recovery of these patients was uncomplicated in all but the one patient who developed delayed gastric emptying. The success rate in terms of resolving the patients' dysphagia was very gratifying, and in those with residual dysphagia, repeat balloon dilatation added further to the overall success rate. Few patients developed recurrent dysphagia and in the majority of these this occurred during the early post-operative period. The overall follow-up period in this study is probably sufficient to predict a low risk of developing dysphagia in the long-term.

This study highlights an important subgroup of patients with intractable dysphagia caused by peri-oesophageal fibrosis after laparoscopic Nissen fundoplication. Early identification of these patients is important in order to avoid prolonged and inappropriate conservative treatment. Pre-operative confirmation of peri-oesophageal fibrosis remains problematic but significant weight loss is an important clinical indicator and can usually be confirmed by either a barium swallow and or endoscopic evaluation.

Appendix 1

Score	Solids	soft food	liquids	chest pain
0 - none				
1 - ≤1/week				
2 - >1/week <daily				
3 daily				
4 - every meal				

Dysphagia: 0 – 12 Chest pain: 0 - 4

Score	regurgitation	heartburn
0 – none		
1 - ≤1/week		
2 - >1/week < daily		
3 – daily		
4 - every meal		

Regurgitation: 0 - 4 Heartburn: 0 - 4

Dysphagia symptom and reflux symptom score

Appendix 2

Questions	
1. How bad is your heartburn?	0 1 2 3 4 5
2. Heartburn when lying down?	0 1 2 3 4 5
3. Heartburn when standing up?	0 1 2 3 4 5
4. Heartburn after meals?	0 1 2 3 4 5
5. Does heartburn change your diet?	0 1 2 3 4 5
6. Does heartburn wake you from sleep?	0 1 2 3 4 5
7. Do you have difficulty swallowing?	0 1 2 3 4 5
8. Do you have pain with swallowing?	0 1 2 3 4 5
9. Do you have gassy or bloating feelings?	0 1 2 3 4 5
10. If you take medication, does it affect your daily life?	0 1 2 3 4 5

GORD-HRQL questionnaire

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